The Immature Cerebellum: How Malformations And Lesions Change Movement, Cognition, And Affect

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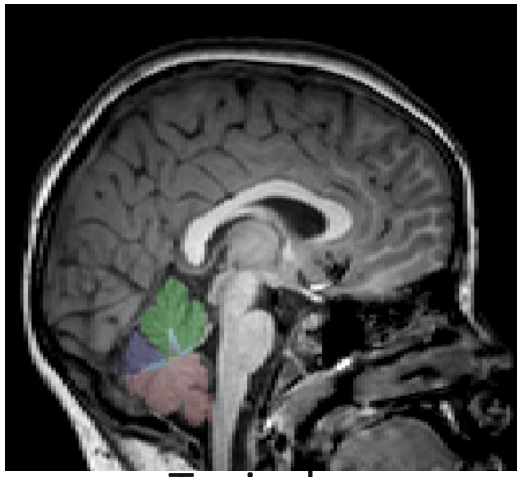
Objectives

- To describe malformations and acquired lesions of the cerebellum.
- To review motor, cognitive, and affective outcomes of childhood cerebellar disorders
  - movement of eyes, upper limbs, hands
  - perceptual and motor timing and rhythm
  - automatic and controlled attention
  - emotion recognition and regulation.
- To consider some issues about structural and functional plasticity of immature cerebellum.

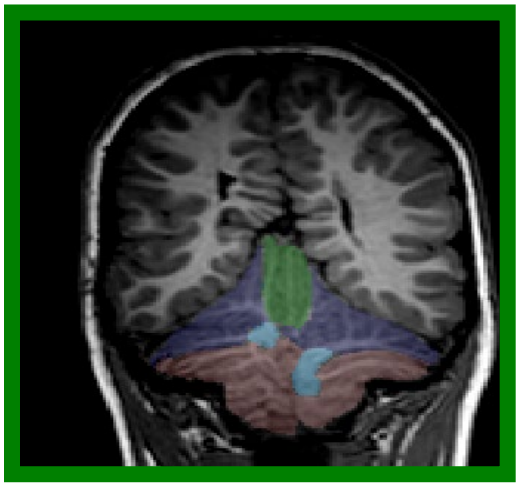
Derailed Cerebellar Development

- Cerebellar development may be derailed in two ways :
  - Developmentally disordered structural plan.
  - Normal plan followed by an acquired lesion at some point in childhood.

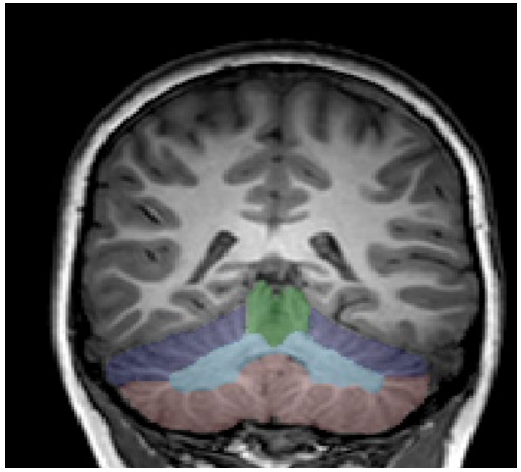
Typical and Aberrant Development

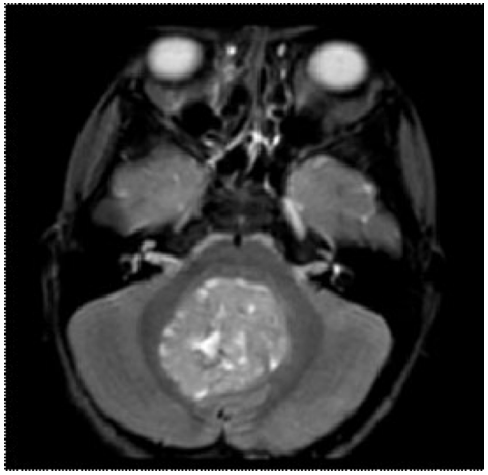


Typical



Aberrant topographical development





Acquired Lesion

Organization Of Workshop

- Developmental cerebellar dysmorphology
  - Cerebellar Structure
  - Cerebellar Function
    - Movement
    - Cognition
    - Affect
  - Clinical Implications
- Childhood-acquired cerebellar lesions
  - Cerebellar Structure
  - Cerebellar Function
    - Movement
    - Cognition
    - Affect
  - Clinical Implications
- Age-Related Cerebellar Plasticity?
  - Structural
  - Functional

Diverse Developmental Disorders Involve The Cerebellum

Developmental cerebellar dysmorphology

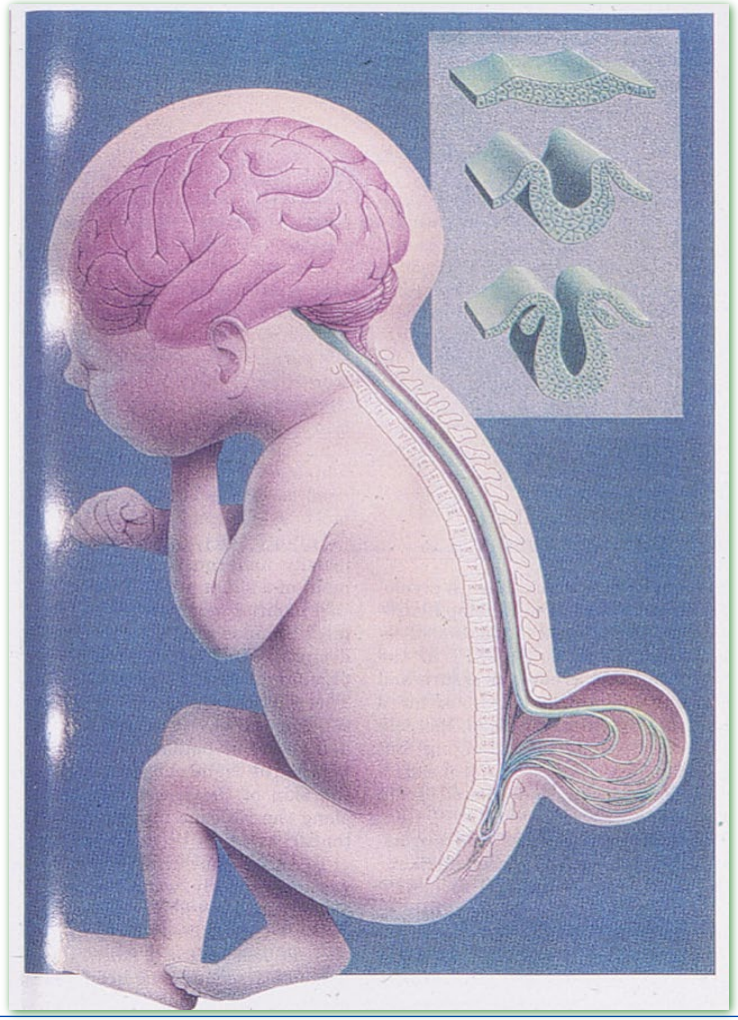
- Spina bifida meningomyelocele
- 22q11.1 Deletion Syndrome
- Autism
- Asperger syndrome
- Williams syndrome
- Down Syndrome
- Fragile X
- Dandy-Walker syndrome & variants
- Joubert syndrome

Acquired cerebellar lesions

- Cerebellar medulloblastoma
- Cerebellar astrocytoma
- Cerebellar strokes
- Traumatic brain injury
- Prematurity
- Alcohol & drug use

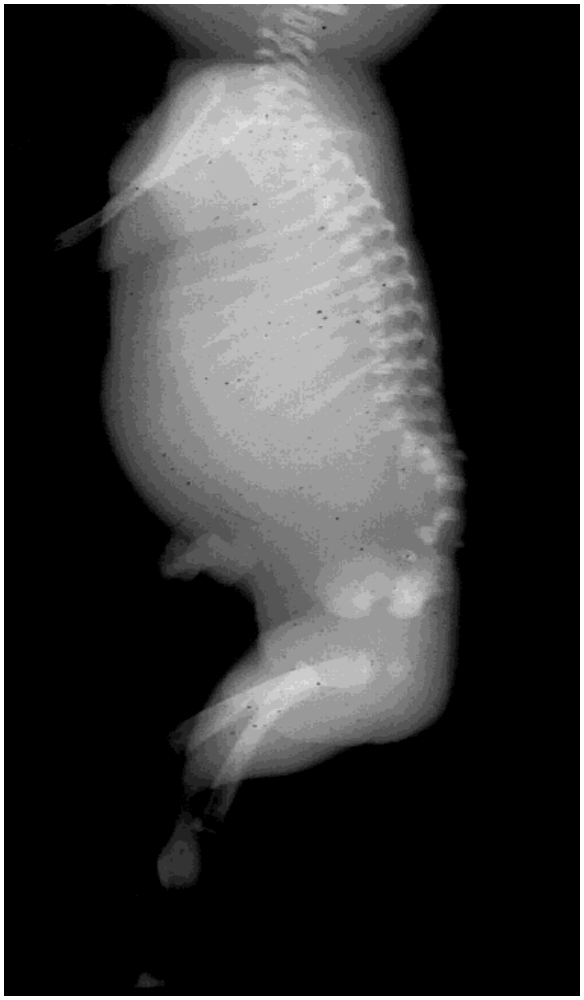
Spina Bifida Meningomyelocele

Spina Bifida



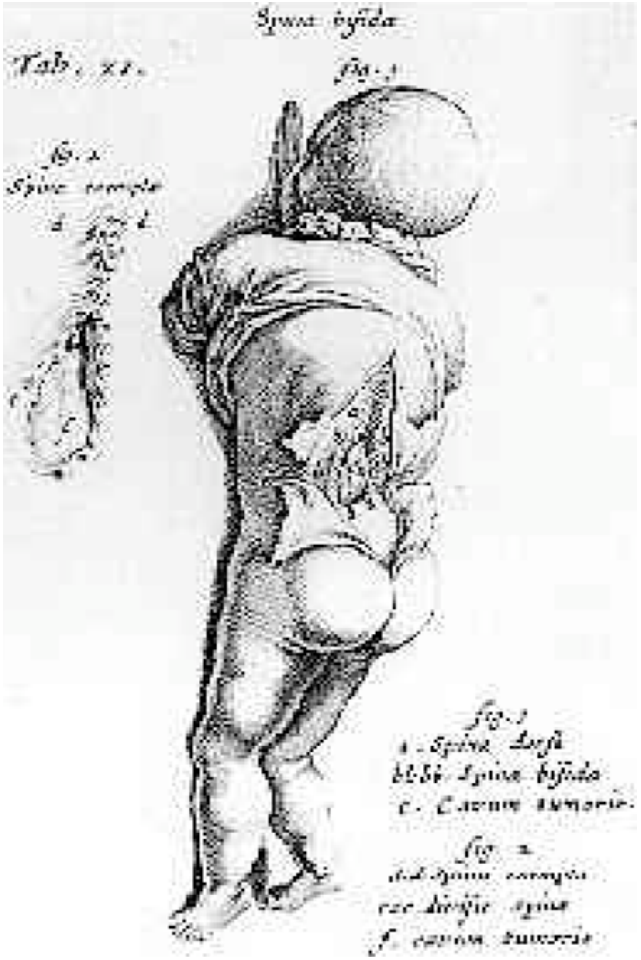
- Most prevalent CNS disorder in children.
- Most common congenital birth defect in North America.
- Failure of embryogenesis: Neural tube does not close around 26-28 days gestation.
- In myelomeningocele (95%) neural groove does not separate from ectoderm, remains exposed on back.
- Lesion anywhere on spine
- Lesion of spine AND BRAIN.

Spina Bifida *in utero*



- Neural tube closes in stages and is normally sealed by the 4th week of gestation
- Fetus, 21 weeks
- Neural tube has not closed, spine is open
- Obvious lower spinal defect, lumbar-sacral area

Tulp (1716)



- Using post-mortem material, Tulp in 1716 described the spinal lesion of meningomyelocele (Koehler, De Wever, & Heerlen, 1996)
- Morgagni in 1761 noted the association between spina bifida and deformities of the lower limbs (Lendon, 1969).

FIG. 2. (left). Tulp's drawing of spina bifida in a patient described in the fifth edition of his work, 1716. (Reproduced by courtesy of the Municipal Hospital, Leyenburg, The Hague, The Netherlands.)

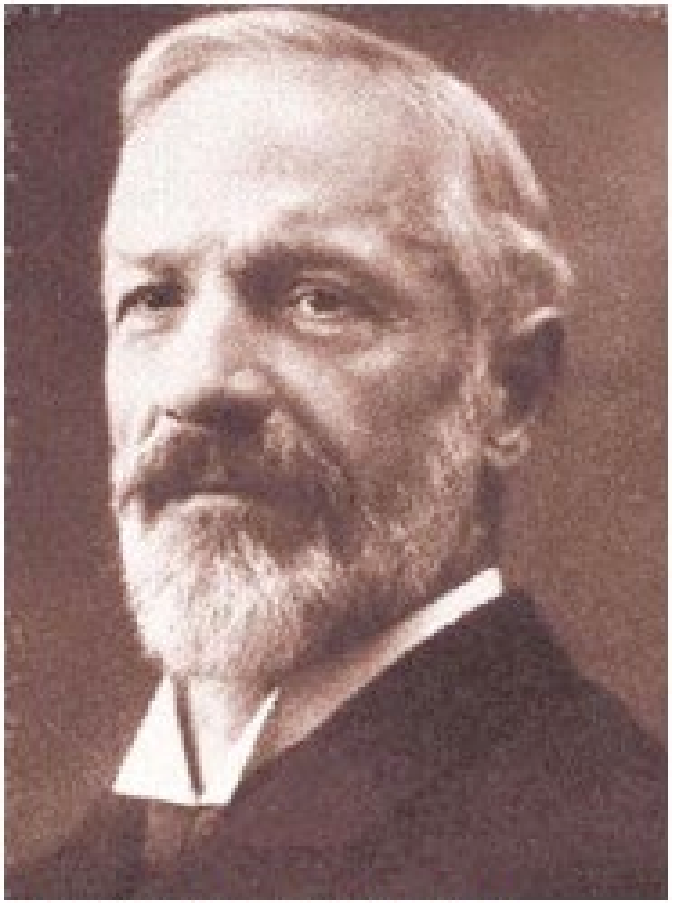
In Spina Bifida And Chiari 11, The Developmental Plan For The Cerebellum And Midbrain Goes Awry

John Cleland (1835-1925)

Fig. 6. Portion of brain and spinal cord. a, corpora quadrigemina; hemispheres of cerebellum; c, extremity of elongated nodule.

- John Cleland studied medicine in Edinburgh and became professor of anatomy in Glasgow.
- In 1883, he described an infant with spina bifida and hydrocephalus.
- The cerebellar lobes were completely divided and nodulus was *inside* the elongated fourth ventricle.
- Cleland linked spinal cord lesion to cerebellar dysmorphologies; differentiated more severe thoracic spinal lesions from less severe lumbar spinal lesions.

Hans Chiari (1851-1916)



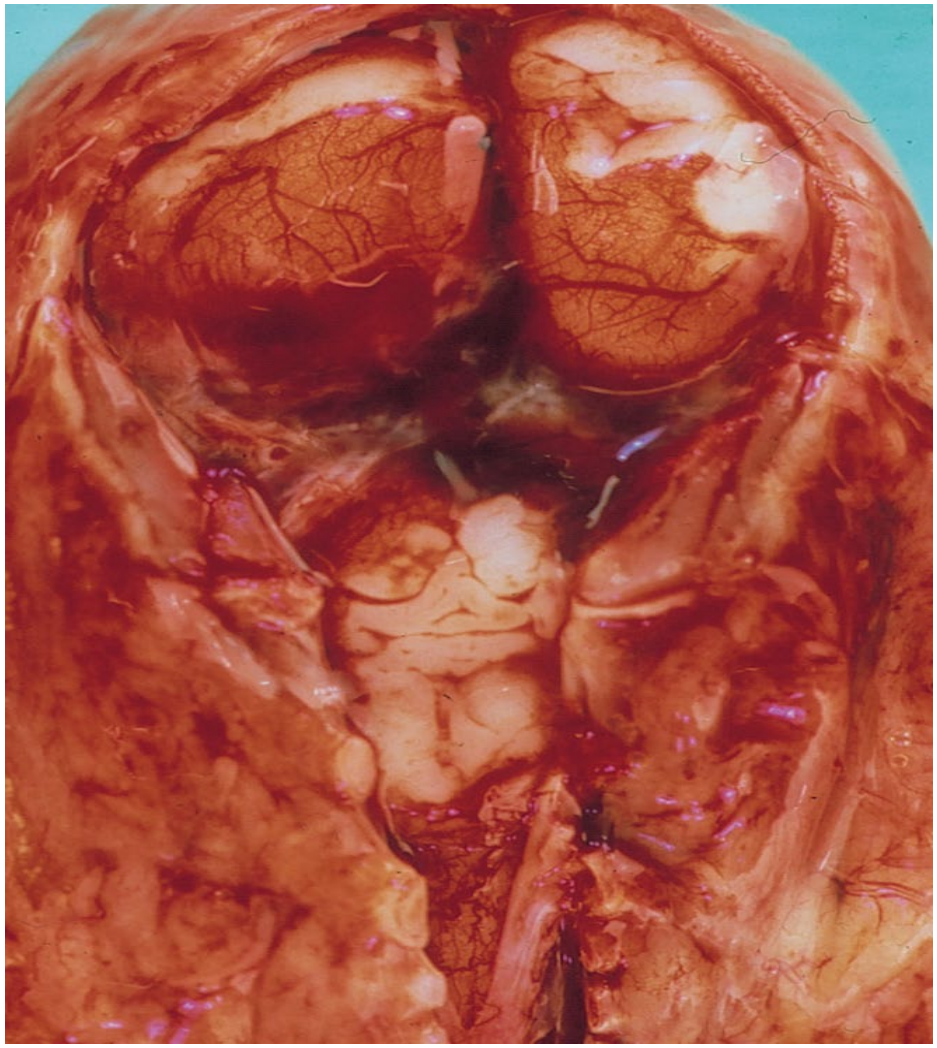
Photograph of Hans Chiari (1851–1916)

- In 1891, Hans Chiari described three grades of cerebellar abnormalities in patients with chronic hydrocephalus, including what is now termed the Chiari type II malformation.

The Chiari II Malformation

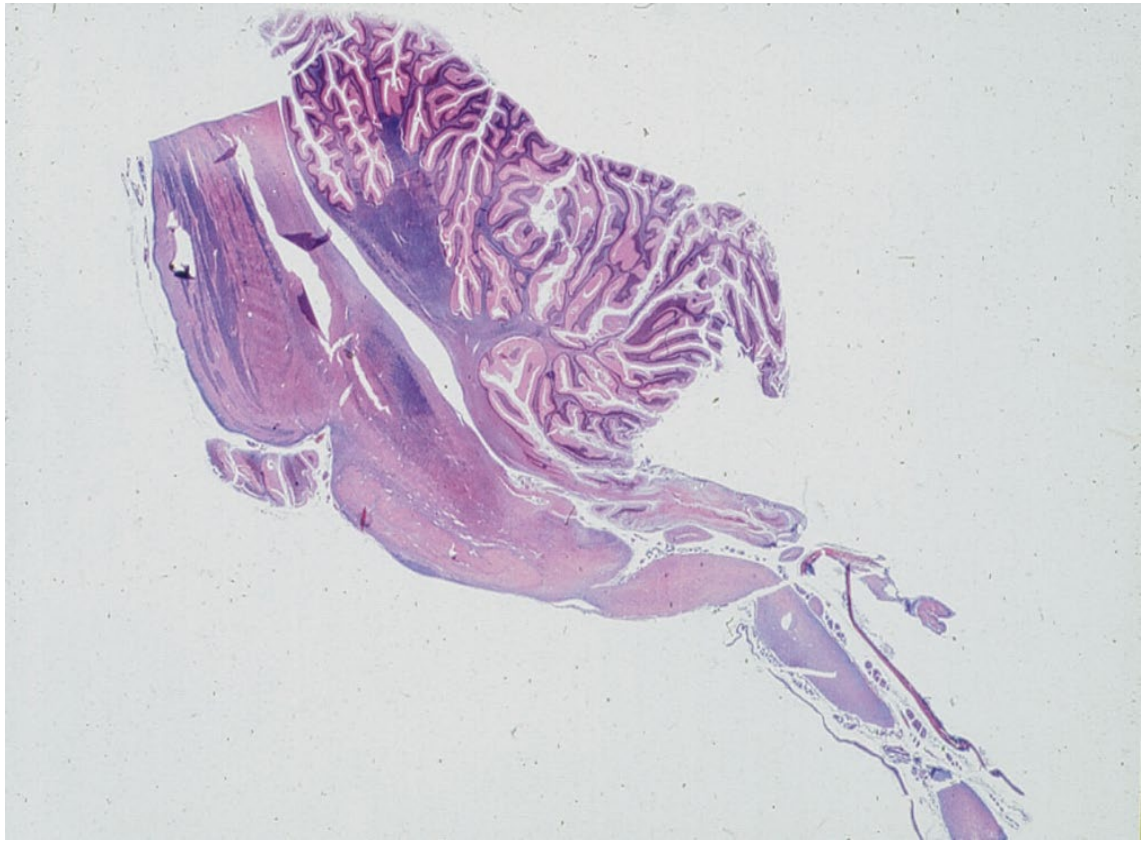
- The Chiari type II malformation, almost universal in neonates born with spina bifida meningomyelocele, is a congenital anomaly of cervical spinal cord, brainstem and cerebellum.
- Other anomalies include elongated cranial nerves, corpus callosum absence or hypogenesis, syringomyelia, neuronal migration defects, hypoplasia of the cranial nerve nuclei, and thalamic deformation.
- Radiological presentation of Chiari II (Raybaud & Miller, 2008):
  - Small posterior fossa causing mechanical abnormalities of medulla.
  - Downward herniation of cerebellum and hindbrain into foramen magnum.
  - Vermis towers above tentorium, producing midbrain abnormalities.

The Chiari II Malformation



- View from back of head, 21-week fetus
- Small posterior fossa
- Small cerebellum
- Herniation of hindbrain (brainstem and cerebellum) below foramen magnum into spinal canal

Chiari II Histology



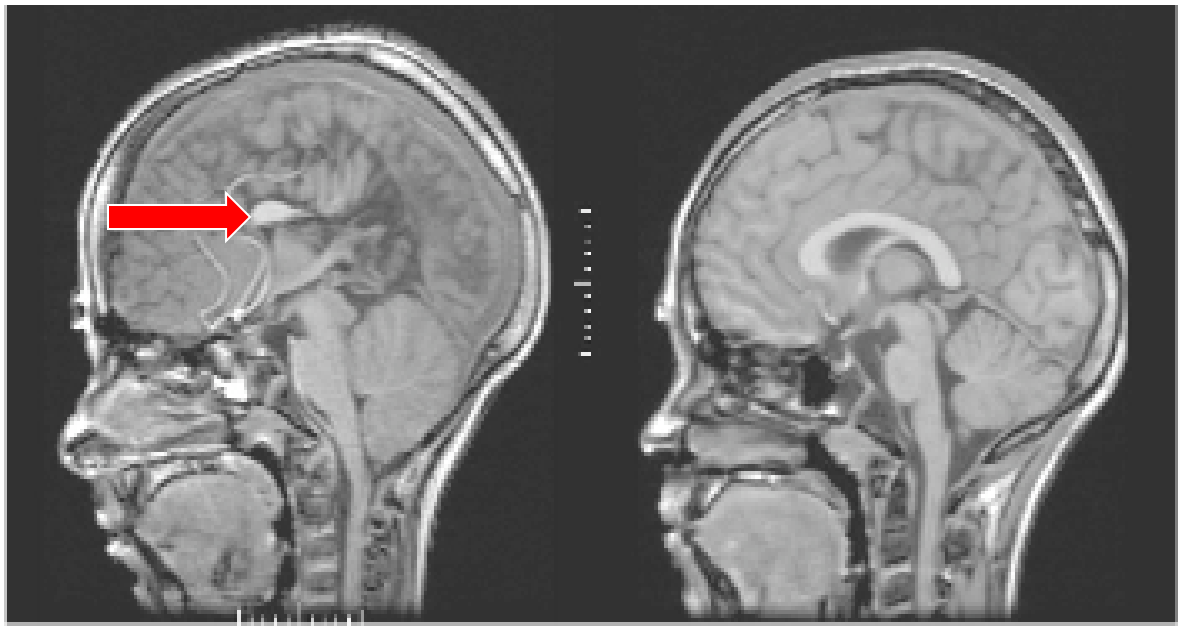
- Tissue block, real size, stain hematoxylin + eosin
- Compressed IV ventricle
- Herniated cerebellar tissue

In Spina Bifida And Chiari 11, The Developmental Plan For Brain Goes Awry

The Reorganized Brain In Spina Bifida

- Massively reorganized, with:
  - Missing regions that should be present.
  - Extra fibre tracts that should be absent.
  - Thin regions that should be fat.
  - Fat regions that should be thin.
  - Normal sculpting that occurs too late.
  - Abnormal sculpting that produces structurally dysmorphic regions.

Absent

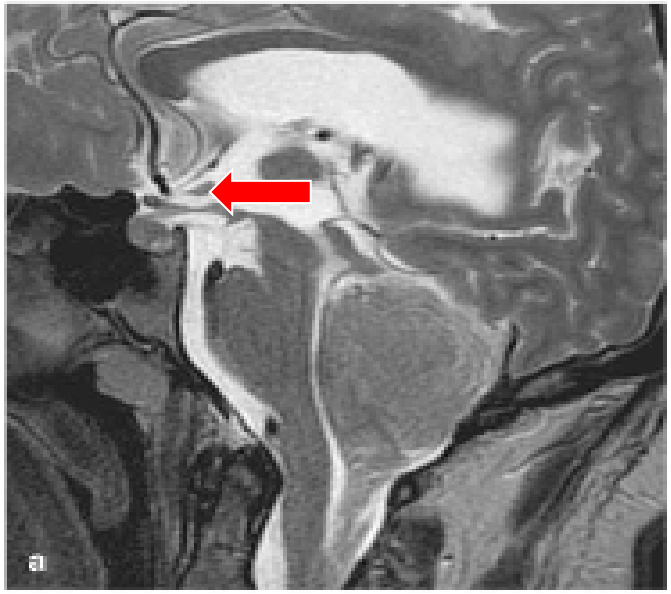


LEFT: missing callosal rostrum, body, splenium
RIGHT: normal

- Children with spina bifida have a high incidence of callosal agenesis.

Aberrant

- Abnormal gray matter structure (hypothalamic adhesion) across anterior-inferior III (48.6%).



- Abnormal white matter bundle (callosal ridge) on dorsal callosum (60%). Aberrant cingulum bundle?

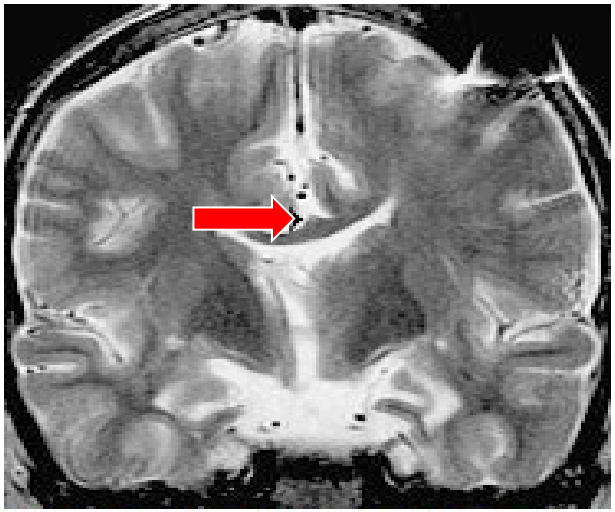


Fig. 6 Callosal ridge. Coronal T2w. Triangular supracallosal longitudinal white matter bundle (*arrow*), presumably aberrant cingular interhemispheric fascicle

(Miller, Widjaja, Blaser, Dennis, Raybaud: *Child's Nervous System*, 2008)

Attenuated

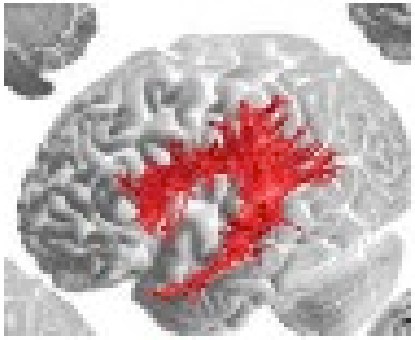
- White matter pathways are significantly attenuated in spina bifida.
  - corticopontocerebellar
  - frontostriatal and thalamofrontal
  - limbic
  - commissural
  - white matter association and projection pathways.

Attenuated Association Pathways

- Abnormal development of association pathways in spina bifida.
  - Poor visualization of tracts
  - Decreased fractional anisotropy
  - Increased diffusivities
  - Impairment in myelination (↑ transverse diffusivity)
  - Abnormalities in intrinsic axonal characteristics and extra axonal/extra cellular space (↑ axial diffusivity).

(Hasan, Eluvathingal, Kramer, Ewing-Cobbs, Dennis, Fletcher: *J. Mag. Res. Imag., 2008)*

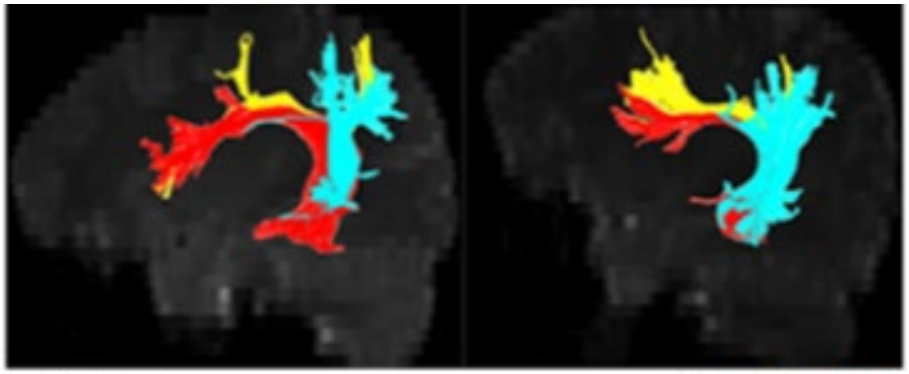
Arcuate Fasciculus



Catani & ffytche, Brain, 2005)
Hasan et al., J Mag Res Imag, 2008

- Long association pathway linking Wernicke + Broca's areas.
- Expanded and left-lateralized in humans.
- Supports transmission of word meaning for sentence comprehension and construction in spontaneous speech.

Segments (fronto-temporal (AFT), fronto-parietal, temporo-parietal.



- Abnormal development in spina bifida: LEFT Arcuate AFT segment less myelinated.
- Arcuate attenuation related to spina bifida language deficits: slow word generation, spontaneous speech dysfluency, poor sentence comprehension?

(Hasan, Eluvathingal, Kramer, Ewing-Cobbs, Dennis, Fletcher: *J. Mag. Res. Imag., 2008)*

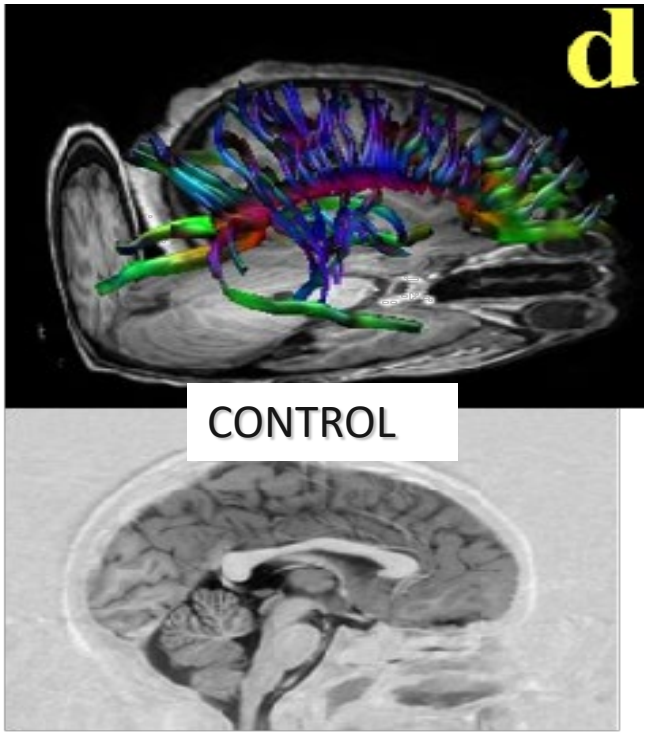
One Part Of The Abnormal Developmental Plan Involves Redistribution of Fibre Tracts And Brain Structures That Are Too Fat

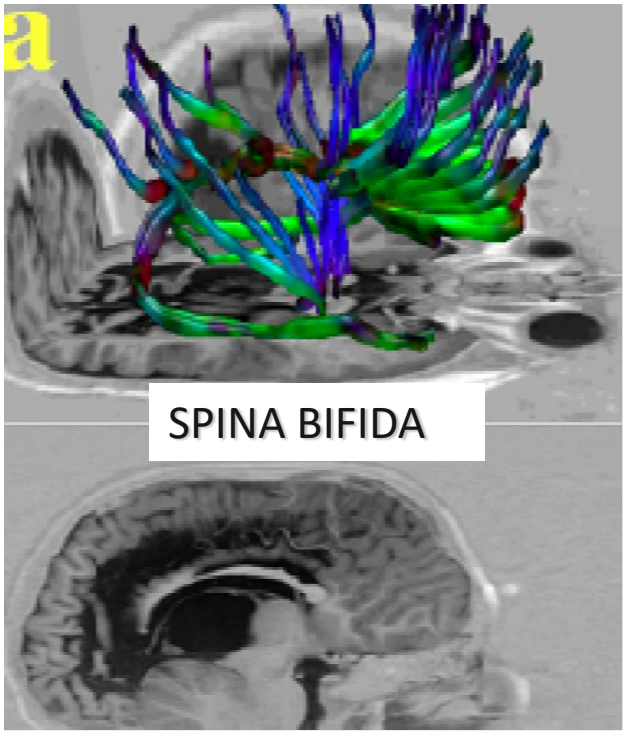
Anterior-Posterior Asymmetry

- Spina bifida cortex is asymmetric in an anterior-posterior (A-P) direction.
  - primary white matter defect
  - effects of hydrocephalus and greater ventricular dilatation in posterior cortex.
- A-P asymmetries and function:
  - Thinner posterior cortex relative to anterior cortex results in Performance IQ<Verbal IQ (Dennis et al., *Arch. Neurol*, 1981. ventriculogram)
  - Thinner posterior cortex associated with poorer visuo-motor, visual perception skills (Fletcher et al., *Arch. Neurol*, 1996, MRI).

Reduced Connectivity On DTI

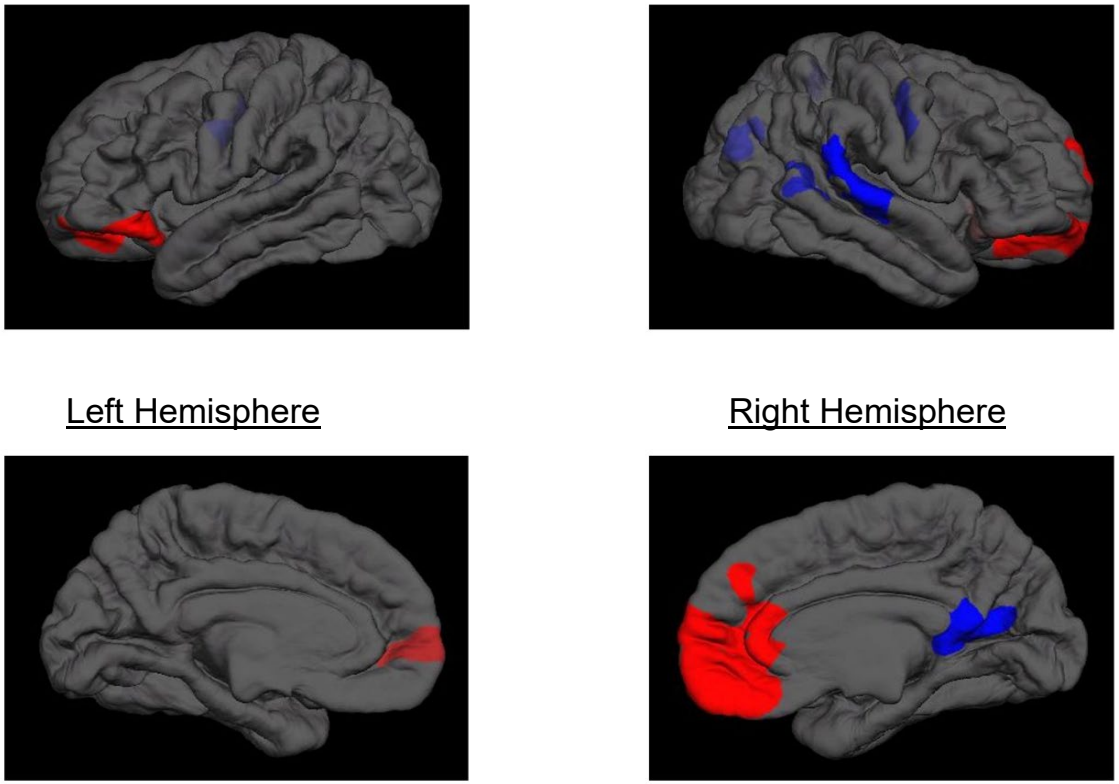
Direction-encoded connectivity (Red=right➔left. Green= anterior➔posterior. Blue=superior➔inferior). Note asymmetric A-P distribution of connectivity in SBM brain.





Montage courtesy of K. Hasan

Posterior Attenuated, Frontal Enhanced

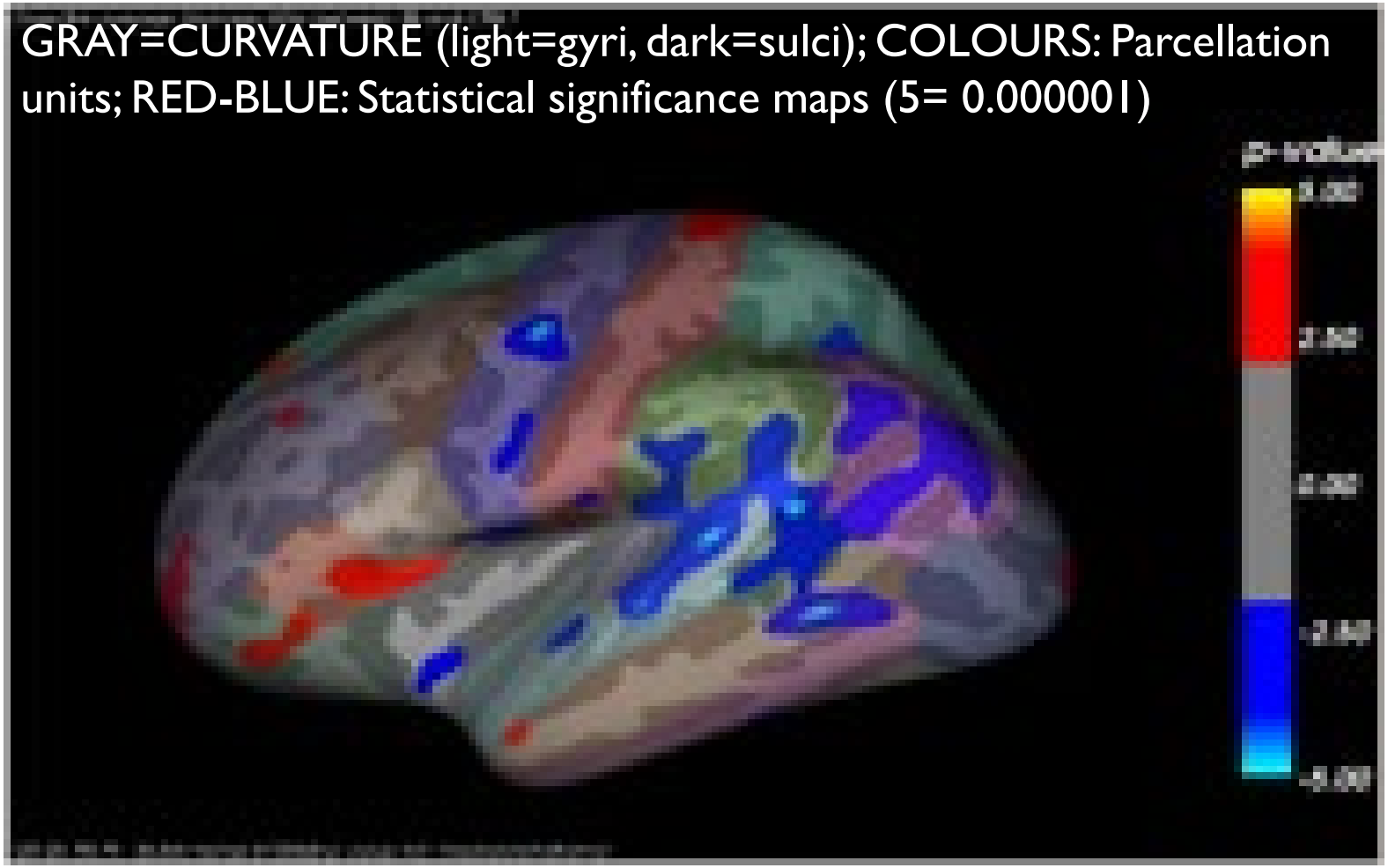


Left Hemisphere

Right Hemisphere

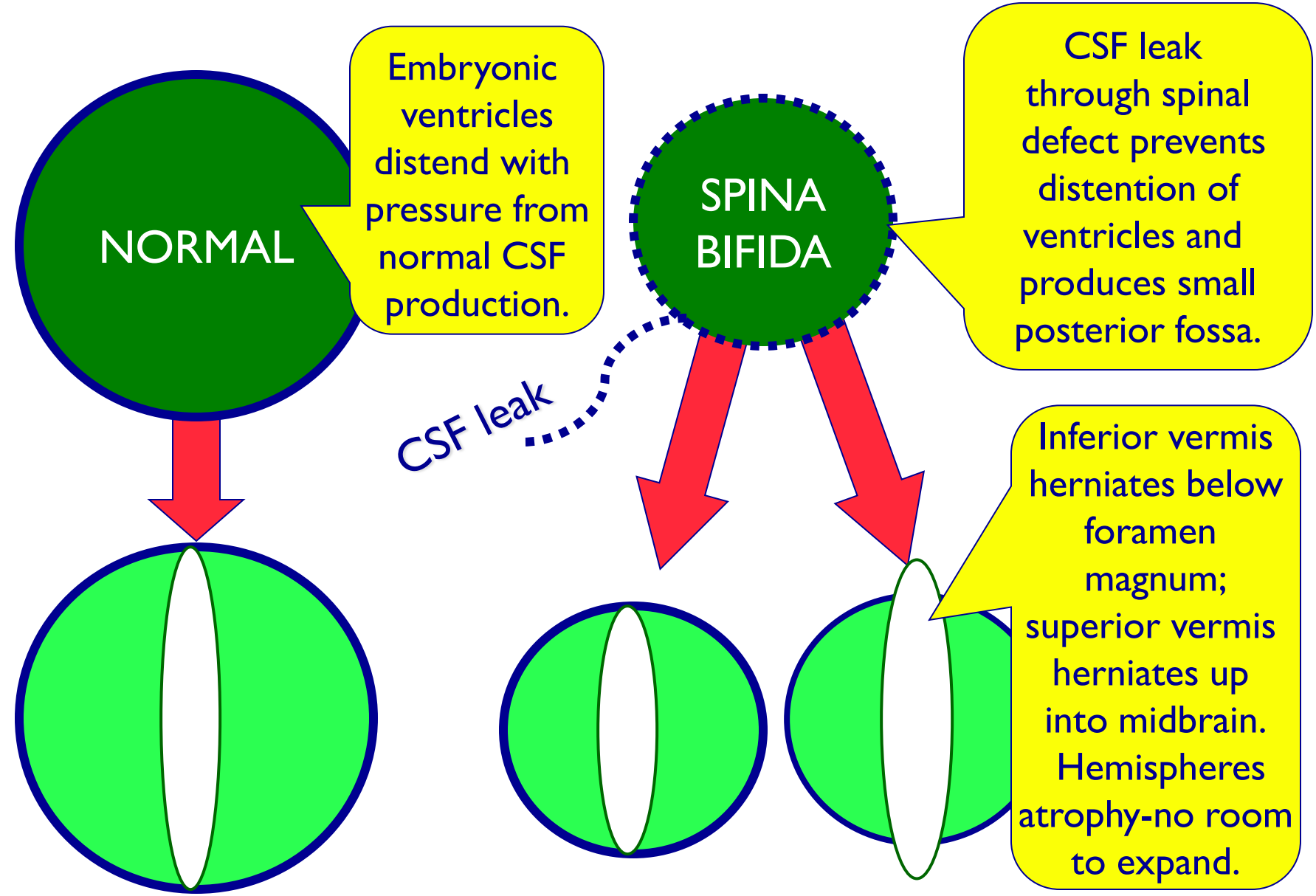
Figure 6: Significant group differences in average cortical thickness displayed on average pial surface of all subjects (n=32): top row=lateral aspect; bottom row=medial aspect. Displayed clusters have been corrected for multiple comparisons: red clusters SB>PC ($p<0.001$); blue clusters indicate SB<PC ($p<0.001$).

Spina Bifida vs. Control Cortical Thickness



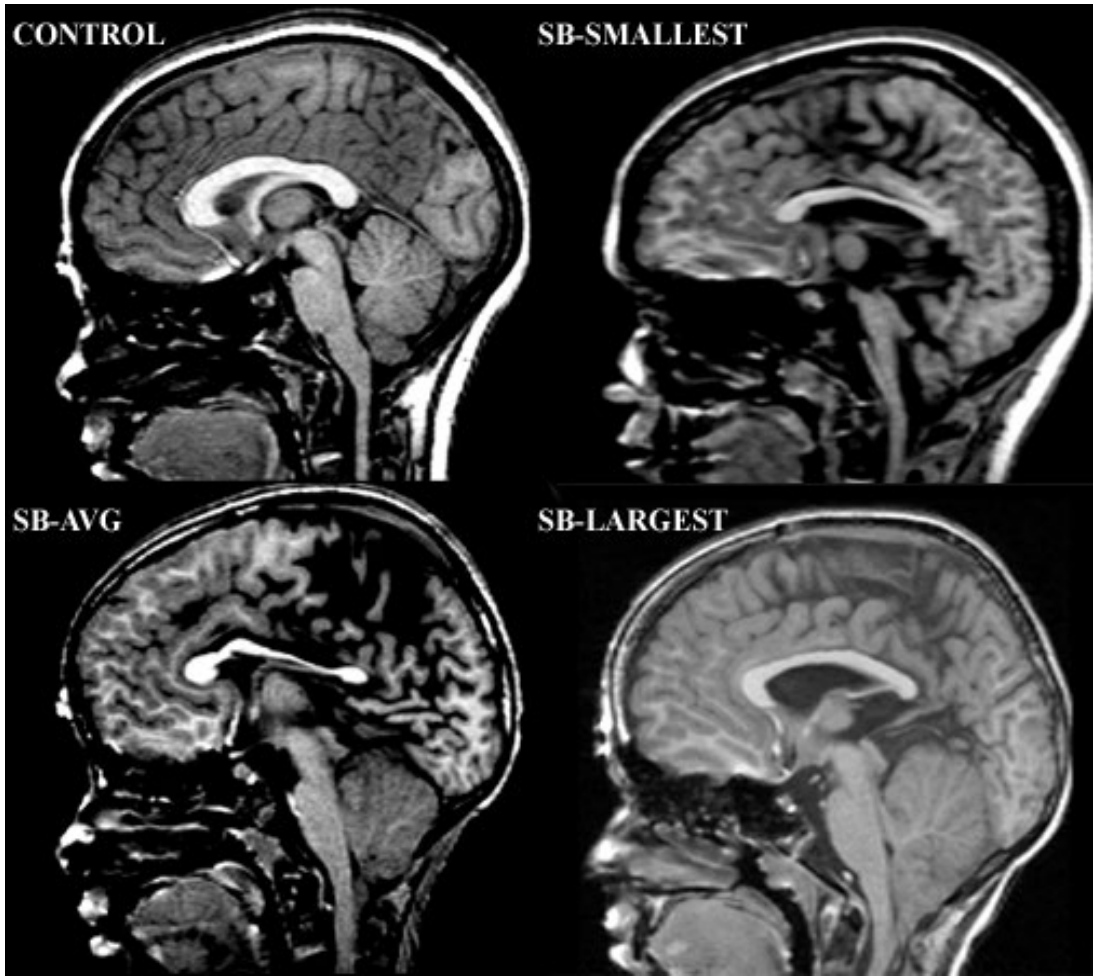
Parcellation figure courtesy J.Juranek

Tissue Redistribution In The Posterior Fossa And Cerebellum: Proposed Mechanism



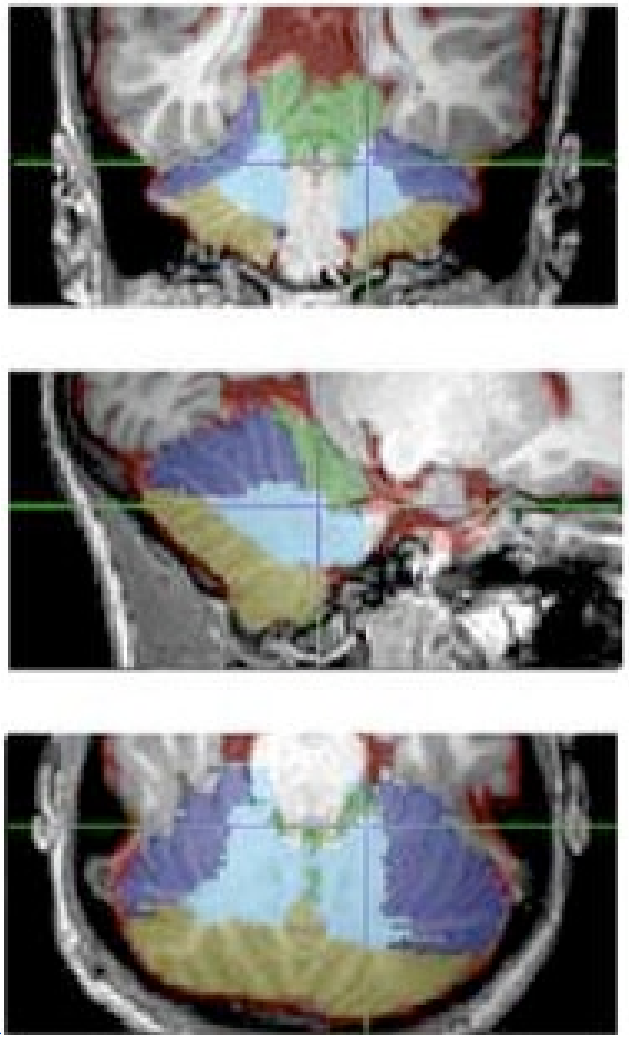
This Means:
A. Cerebellar Variability Across Individuals
B. Cerebellar Variability Within Individuals

Cerebellar Macrostructure: Individual Differences



- Total cerebellar volume reduced.
- Significant group variability in cerebellar volume.

Cerebellar Macrostructure: Parcellation



- A four-compartment model (one WM and three principally GM) parcellated cerebellum into:

1)Corpus medullare (light blue) : central white matter and output nuclei

2)Anterior lobe (green) lobules I-V, bounded by the most posterior point of fourth ventricle, corpus medullare, and primary fissure

3)Superior posterior lobe (dark blue): lobe VI and crus I of VIIA, bounded by primary fissure, corpus medullare, and horizontal fissure

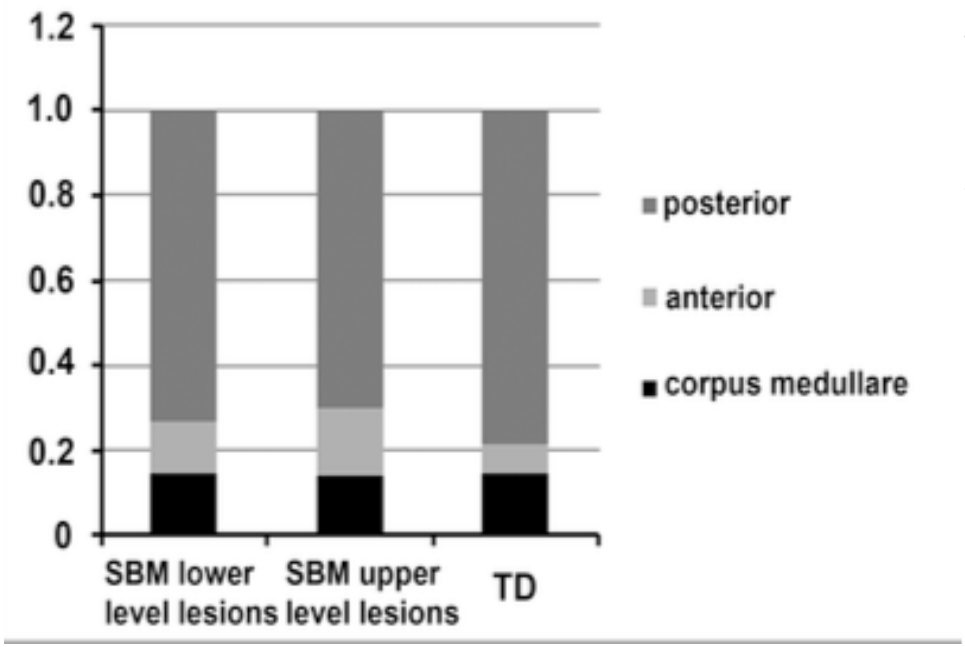
4)Inferior posterior lobe (khaki): crus II of VIIA, VIIB, VIII, IX, X, bounded by the most posterior point of the fourth ventricle, corpus medullare, and horizontal fissure.

5)White is brainstem.

- Spatial transform to standardized template not implemented.

(Juranek, Dennis, Cirino, El-Messidi, Fletcher: *The Cerebellum*, 2010)

Cerebellum Parcellation In Spina Bifida



- Total cerebellar volume reduced.
- Comparisons by compartment as % of total cerebellum volume (left).
- After correcting for total cerebellum volume, and relative to controls, posterior lobe was significantly *reduced* in SBM, corpus medullare was *not different*, and anterior lobe was *enlarged*.
- Reduction in cerebellar volume in SBM group involves a reconfiguration involving anterior lobe enlargement and posterior lobe reduction.

(Juranek, Dennis, Cirino, El-Messidi, Fletcher: *The Cerebellum*, 2010)